

Amendments to the Specification

Please amend the paragraph beginning on page 2, line 10 as follows:

B1 Various molecules in the TNF family also have purported role(s) in the function or development of the immune system [~~Gruss et al.~~ Gruss and Dower, Blood, 85:3378 (1995)]. Zheng et al. have reported that TNF-" is involved in post-stimulation apoptosis of CD8-positive T cells [Zheng et al., Nature, 377:348-351 (1995)]. Other investigators have reported that CD30 ligand may be involved in deletion of self-reactive T cells in the thymus [Amakawa et al., Cold Spring Harbor Laboratory Symposium on Programmed Cell Death, Abstr. No. 10, (1995)]. CD40 ligand activates many functions of B cells, including proliferation, immunoglobulin secretion, and survival [Renshaw et al., J. Exp. Med., 180:1889 (1994)]. Another recently identified TNF family cytokine, TALL-1 (BlyS), has been reported, under certain conditions, to induce B cell proliferation and immunoglobulin secretion. [Moore et al., supra; Schneider et al., supra; Mackay et al., J. Exp. Med., 190:1697 (1999)] ~~MA~~

Please amend the paragraph beginning on page 2, line 25 as follows:

B2 - ~~MA~~ Mutations in the mouse Fas/Apo-1 receptor or ligand genes (called lpr and gld, respectively) have been associated with some autoimmune disorders, indicating that Apo-1 ligand may play a role in regulating the clonal deletion of self-reactive lymphocytes in the periphery [Krammer et al., Curr. Op. Immunol., 6:279-289 (1994); ~~Nagata et al.~~ Nagata and Golstein, Science, 267:1449-1456 (1995)]. Apo-1 ligand is also reported to induce post-stimulation apoptosis in CD4-positive T lymphocytes and in B lymphocytes, and may be involved in the elimination of activated lymphocytes when their function is no longer needed [Krammer et al., supra; Nagata et al., supra]. Agonist mouse monoclonal antibodies specifically binding to the Apo-1 receptor have been reported to exhibit cell killing activity that is comparable to or similar to that of TNF-" [Yonehara et al., J. Exp. Med., 169:1747-1756 (1989)]. ~~MA~~

Please amend the paragraph beginning on page 3, line 1 as follows:

B3 ~~MA~~ Induction of various cellular responses mediated by such TNF family cytokines is believed to be initiated by their binding to specific cell receptors. Previously, two distinct TNF receptors of

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approximately 55-kDa (TNFR1) and 75-kDa (TNFR2) were identified [~~Hohman~~ Hohmann et al., J. Biol. Chem., 264:14927-14934 (1989); Brockhaus et al., Proc. Natl. Acad. Sci., 87:3127-3131 (1990); EP 417,563, published March 20, 1991; Loetscher et al., Cell, 61:351 (1990); Schall et al., Cell, 61:361 (1990); Smith et al., Science, 248:1019-1023 (1990); Lewis et al., Proc. Natl. Acad. Sci., 88:2830-2834 (1991); Goodwin et al., Mol. Cell. Biol., 11:3020-3026 (1991)]. Those TNFRs were found to share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions. The extracellular portions of both receptors were found naturally also as soluble TNF-binding proteins [Nophar, Y. et al., EMBO J., 9:3269 (1990); and Kohno, T. et al., Proc. Natl. Acad. Sci. U.S.A., 87:8331 (1990); Hale et al., J. Cell. Biochem. Supplement 15F, 1991, p. 113 (P424)]. -M

Please amend the paragraph beginning on page 4, line 12 as follows:

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M More recently, other members of the TNFR family have been identified. In ~~von Bulow et al.~~, von Bulow and Bram, Science, 278:138-141 (1997), investigators describe a plasma membrane receptor referred to as Transmembrane Activator and CAML-Interactor or "TACI". The TACI receptor is reported to contain a cysteine-rich motif characteristic of the TNFR family and to be present on both B cells and activated T cells. In an in vitro assay, cross linking of TACI on the surface of transfected Jurkat cells with TACI-specific antibodies led to activation of NF-KB. [see also, WO 98/39361 published September 18, 1998]. -M

Please amend the paragraph beginning on page 6, line 1 as follows:

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-M A further group of recently identified receptors are referred to as "decoy receptors," which are believed to function as inhibitors, rather than transducers of signaling. This group includes DCR1 (also referred to as TRID, LIT or TRAIL-R3) [Pan et al., Science, 276:111-113 (1997); Sheridan et al., Science, 277:818-821 (1997); ~~McFarlane et al.~~, MacFarlane et al., J. Biol. Chem., 272:25417-25420 (1997); Schneider et al., FEBS Letters, 416:329-334 (1997); Degli-Esposti et al., J. Exp. Med., 186:1165-1170 (1997); and Mongkolsapaya et al., J. Immunol., 160:3-6 (1998)] and DCR2 (also called TRUND or TRAIL-R4) [Marsters et al., Curr. Biol., 7:1003-1006 (1997); Pan et al., FEBS Letters,

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424:41-45 (1998); Degli-Esposti et al., *Immunity*, 7:813-820 (1997)], both cell surface molecules, as well as OPG [Simonet et al., *supra*; Emery et al., *infra*] and DCR3 [Pitti et al., *Nature*, 396:699-703 (1998)], both of which are secreted, soluble proteins. *W*

Please amend the paragraph beginning on page 6, line 23 as follows:

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Please amend the paragraph beginning on page 85, line 8 as follows:

88 To identify a receptor for TALL-1, a cDNA expression library was constructed in pRK5 vector (EP 307,247, published March 15, 1989) using PolyA+ mRNA derived from the IM-9 cells [~~Flanagan et al.~~, Flanagan and Leder, Cell, 63:185 (1990)]. Pools of ~1000 cDNA clones (Miniprep DNA (Qiagen)) from the library were transfected (using Lipofectamine) into COS 7 cells (ATCC) in 6 well plates, which after 36-48 hours, were then incubated with AP-TALL-1 conditioned medium, washed, and stained for AP activity in situ. A positive pool was broken down to successively smaller size pools. After three rounds of screening, a single cDNA encoding an AP-TALL-1 binding activity was identified. Sequencing of the cDNA insert revealed a single open reading frame predicted to encode a protein of 265 amino acids. This 265 amino acid polypeptide (referred to as "hTACI (265)" in Figure 6), when aligned with the TACI sequence shown in Fig. 1 (referred to as "hTACI" in Figure 6), revealed a high percentage of sequence identity, particularly in the ECD. The alignment of these two TACI sequences is shown in Figure 6. It is believed that the 265 amino acid form of TACI may be a spliced variant of the TACI sequence shown in Figure 1. - -

Please amend the paragraph beginning on page 91, line 13 as follows:

89 - During the early part of an antigen-specific antibody response, B cells differentiate into antibody-forming cells (AFC). This takes place in extrafollicular areas of the spleen composed of periarteriolar lymphoid sheaths (PALS) [~~Gray et al.~~, Gray, D., Immunology, 65:73 (1988); ~~NaeLennan~~, MacLennan, Ann. Rev. Immunol., 12:117 (1988 1994)], where Ig class switching subsequently occurs. The PALS-associated regions were compared from spleens of NP23-CgG-immunized mice treated for 10 days with control Ig, TACI-Fc, or BCMA-Fc, similar to as described above. Immunohistochemical analysis of the various spleen sections was then conducted. Spleen sections prepared 10 days after immunization and stained with FITC-conjugated anti-IgG1 are shown in Figure 13-1 (Panel A) and Figure 13-2 (Panel A). As expected, control mice displayed a large number of clustered AFC foci that stained intensely with anti-IgG1 and contained many immunoblast-like cells (Fig. 13-1, Panel A, left). In contrast, TACI-Fc treated mice showed only few, isolated, IgG1-positive cells, with no formation of AFC

CP 9 foci (Fig. 13-1, Panel A, right). BCMA-Fc treated mice likewise showed only few, isolated, IgG1-positive cells, with no formation of AFC foci (Fig. 13-2, Panel A). Thus, TALL-1/TACI and TALL-1/BCMA (and APRIL/TACI and APRIL/BCMA) interactions are important for the extrafollicular differentiation of B cells that precedes Ig class switching in splenic PALS-associated areas. -

Please amend the paragraph beginning on page 92, line 19 as follows:

10 The blocking of the TALL-1/TACI and TALL-1/BCMA interactions (or APRIL/TACI or APRIL/BCMA interactions) in mice during primary immunization inhibited several aspects of the B cell response: (a) the early phase of extrafollicular B cell activation that leads to antigen-specific IgM production; (b) the differentiation of B cells that leads to Ig class switching; (c) the formation of splenic GCs, where affinity maturation occurs and memory B cells are generated. While GC formation was blocked completely by TACI-Fc or BCMA-Fc, some residual IgM and IgG1 production and affinity maturation occurred. That attenuated antibody responses can proceed despite the absence of GCs has been observed in other systems [see, e.g., Matsumoto et al., Nature, 382:462 (1996); Kato et al., J. Immunol., 160:4788 (1998); Futterer Futterer et al., Immunity, 9:59 (1998)]. It is possible that other factors besides TALL-1 or APRIL and TACI or BCMA mediate the remaining antibody production. Alternatively, the selected TACI-Fc or BCMA-Fc treatment in vivo may not have sufficed to prevent all TALL-1/TACI, TALL-1/BCMA, APRIL/TACI or APRIL/BCMA binding events.

Please amend the paragraph beginning on page 92, line 36 as follows:

B Previous studies indicate that CD40L-CD40 [Foy et al., Ann. Rev. Immunol., 14:591 (1996)] and CD86-CD28/CTLA-4 [Han et al., J. Immunol., 155:556 (1995); Lenschow et al., Ann. Rev. Immunol., 14:233 (1996)] interactions are important for entry of extrafollicular B cells into GC areas and for GC establishment. Inhibition of these interactions through gene knockouts or by treatment with blocking antibodies or receptor-Fc fusions diminishes antibody production and blocks GC formation [Lane et al., J. Exp. Med., 179:819 (1994); Durie et al., Immunol. Today, 15:406 (1994); Hathcock et al., Science, 262:905 (1993); Linsey Linsley et al., Science, 257:7992 792 (1992); Renshaw et al., J. Exp.

812. Med., 180:1889 (1994); Xu et al., Immunity, 1:423 (1994); Kawabe et al., Immunity, 1:167 (1994); Foy et al., J. Exp. Med., 180:157 (1994)]. There are some striking similarities between the TALL-1/TACI, TALL-1/BCMA and CD40L-CD40 systems: both ligands are related to TNF and are expressed on activated T cells and both receptors are TNFR homologs that stimulate NF-KB and are expressed on B cells. Hence, the interaction of TALL-1 or APRIL with TACI or BCMA might mediate T-cell help to B cells similar to CD40L and CD40. TALL-1 also may contribute to the activation of B cells by dendritic cells, which do express the TALL-1 ligand. Unlike CD40L and CD40 knockout mice, which exhibit impaired IgG but not IgM responses, and unlike CD40L-deficient patients with hyper-IgM syndrome [Callard et al., Immunol. Today, 14:559 (1993); Allen et al., Science, 259:990 (1993); Aruffo et al., Cell, 72:291 (1993)], TACI-Fc-treated or BCMA-Fc-treated mice showed a marked deficit in both IgM and IgG production. Thus, it is possible that TALL-1 or APRIL and TACI or BCMA operate early in B cell activation, such that their blockade impairs all phases of the humoral response. In contrast, CD40L and CD40 may operate later in B cell activation, such that their blockade impairs only late phases of the antibody response.

Please amend the paragraph beginning on page 96, line 9 as follows:

813. - To determine whether the anti-APRIL antibodies, 3C6.4.2, 5E8.7.4, 5E11.1.2 and 5G8.2.2 (described in the Examples above) recognized the same or different epitopes, a competitive binding ELISA was performed as described in Kim et al., J. Immunol. Methods, 156:9-17 (1992) using biotinylated anti-APRIL antibodies. The anti-APRIL monoclonal antibodies were biotinylated using N-hydroxyl succinimide as described in Kim et al., J. Immunol. Methods, 156:9-17 (1992). Microtiter wells were coated with 50ml of 0.5mg/ml of Flag-APRIL (Example 2) in 50mM carbonate buffer, pH 9.6, overnight at 4°C. After washing, the nonspecific binding sites were blocked with 200ml of 2% BSA for 1 hour. After washing, a mixture of a predetermined optimal concentration of biotinylated anti-APRIL antibodies and a 100-fold excess of unlabeled monoclonal antibodies were added to each well. Following a 1 hour incubation at room temperature, plates were washed and the amount of biotinylated anti-APRIL antibody was detected by the addition of HRP-streptavidin. After washing the

3/3 microtiter wells, the bound enzyme was detected by the addition of substrate, and the plates were read at 450nM with an ELISA plate reader. *3/7* -

Please amend the paragraph beginning on page 103, line 35 as follows:

8/4 - *3/7* In Applicants' study, two groups of 10 mice each (10 to 15 week old male and female MBP-TCR transgenic mice (described in Example 10) were immunized subcutaneously with 10 µg MBP Acl-11 (described in Example 10 above) in 100 µl complete Freund's adjuvant (CFA) (Difco). Following the initial immunization with Acl-11, 200 ng Pertussis toxin (List Biologicals, Campbell, CA) in 100 µl saline was injected intraperitoneally in each mouse at 24 hours and 48 hours. Starting on day 2 through day 24, one group of mice was injected with 100 µg of TACI-Fc (described in Example 10) in 100 µl sterile saline intraperitoneally daily, and a second group received 100 µg of murine IgG in 100 µl sterile saline intraperitoneally each day. Animals were then monitored daily for the onset of disease. Clinical signs of experimental allergic encephalomyelitis (EAE) were assessed daily and a score of 1 to 5 was given to each mouse based on the established EAE index system: 0= normal appearance; 1= tail droop; 2= abnormal gait; 3= limb weakness; 4= paralysis involving one limb (partial hindlimb paralysis); 5= paralysis involving two limbs (total hindlimb paralysis). This is a modified scoring system from that previously described in Grewal et al., Science, 273:1864-1867 (1996). *3/7* -
